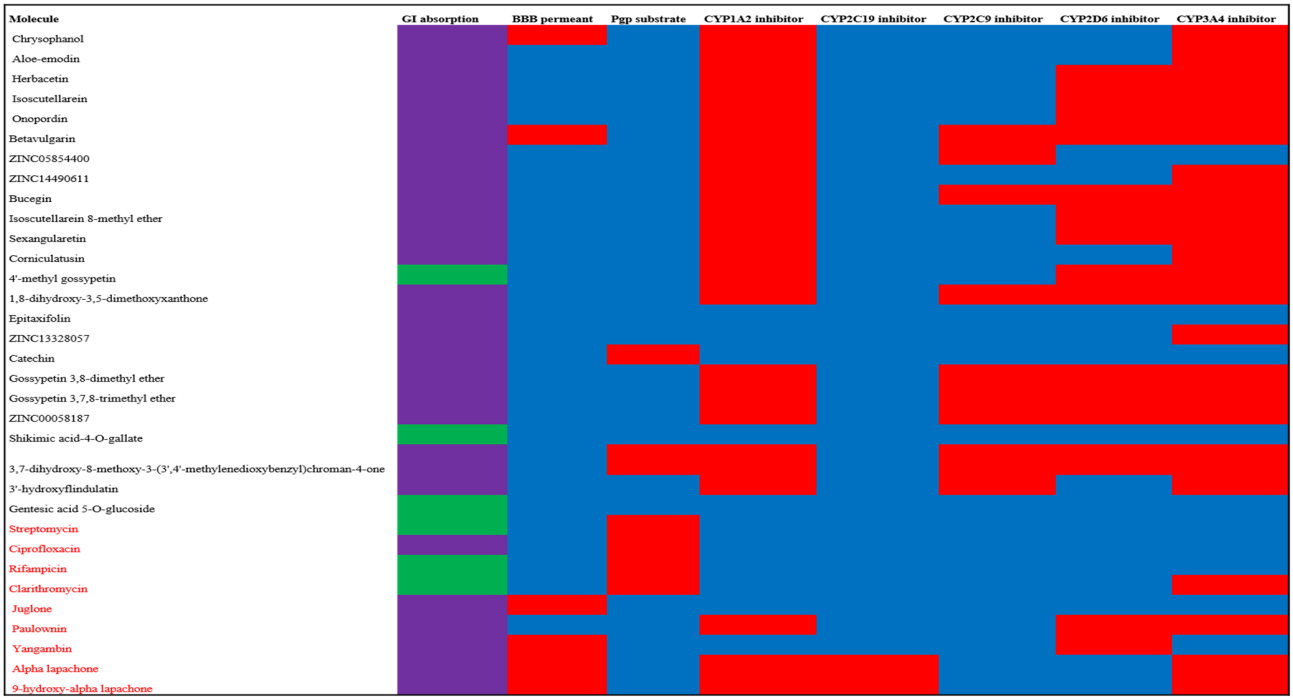

Figure S1. A heat map showing the pharmacokinetic properties of potential leads, known drugs and inhibitors predicted as GI absorption, BBB permeant, and Pgp substrate, as well as CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 inhibitors. Red denote "Yes" whilst blue denotes "No" to cytochrome inhibition, respectively. Also, low Gastrointestinal (GI) absorption is denoted by green, whilst high denoted by violet.

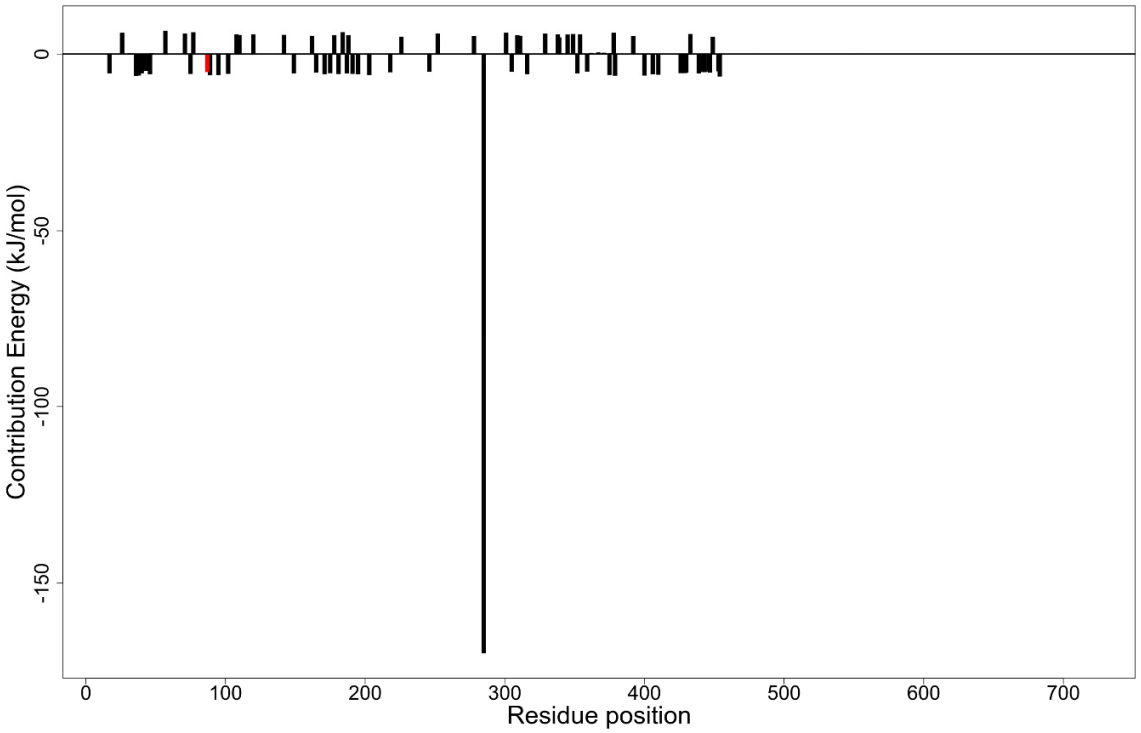

Figure S2. Molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) plot of binding free energy contribution per residue of Gentesic 5-O glucoside complex. Fluctuations by hitherto predicted critical residues are shown in red.

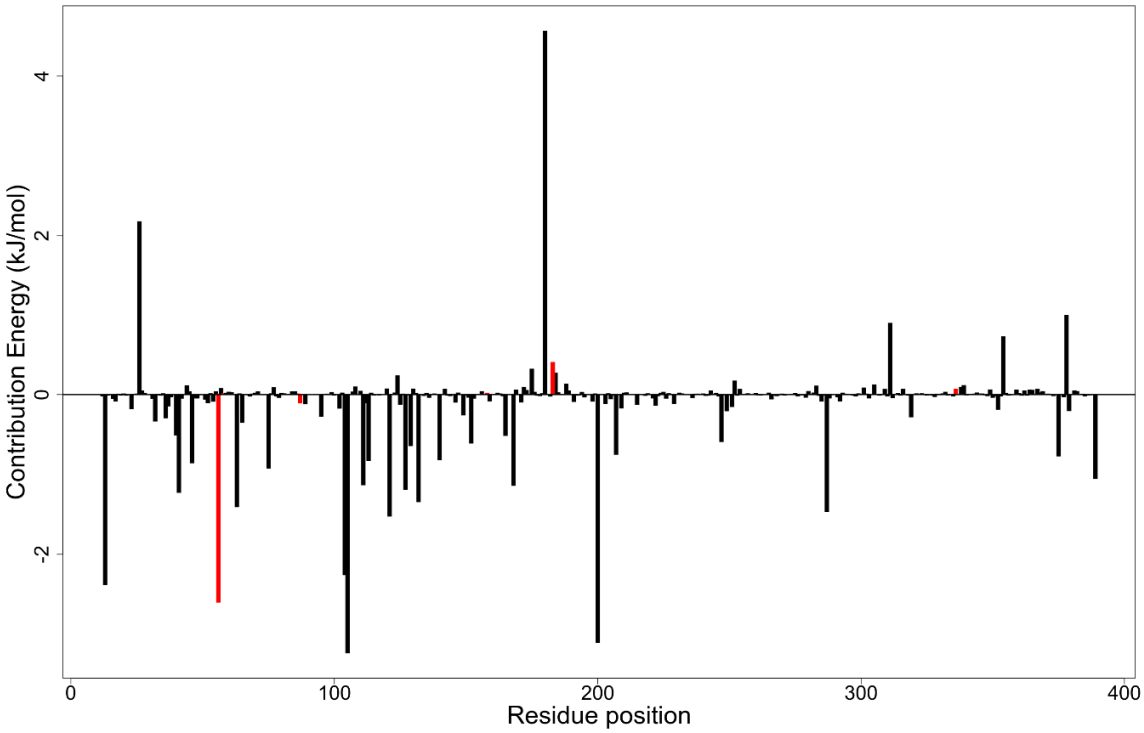

Figure S3. Molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) plot of binding free energy contribution per residue of Isoscutellarein complex. Fluctuations by hitherto predicted critical residues are shown in red.

Table S1. The interaction studies of the top 24 pharmacophore hit compounds following molecular docking arranged in descending order of the number of hydrogen bonds formed. Known inhibitors are in red.

ZINC ID/ COMPOUND NAME	Binding energies (Kcal/mol)	Interacting residues in the active binding site	Number of hydrogen bonds	Length of the hydrogen bonds (Å)	Number of hydrophobic interactions	Total number of bonds
Shikimic acid-4-O-gallate	-7.6	Ser85, Gly86, Tyr111, Asp183 Ser205,	6	3.13[Ser85], 3.11[Gly86], 2.87[Tyr111], 2.90[Asp183], 3.00, 3.06[Ser205]	4	10
Epitaxifolin	-8.1	Gly86, Met87, Asn158, Asp183, Ser205	5	3.10[Gly86], 2.99[Met87], 2.80[Asn158], 3.11[Asp183], 3.12[Ser205]	7	12

Gentisic acid 5-O-glucoside	-7.1	Thr114, Asp183, Thr207	5	3.27[Thr114], 2.71, 2.72[Asp183], 3.00, 3.02[Thr207]	8	12
Betavulgarin	-8.4	Gly86, Asn158, Ser205, Thr207	4	3.14[Gly86], 2.93[Asn158], 3.07[Ser205], 2.75[Thr207]	9	13
Paulownin	-8.5	Gly86, Tyr111, Ser205, Thr207	4	3.21[Gly86], 2.75[Tyr111], 2.75[Ser205], 2.94[Thr207]	3	7
Isoscutellarein	-8.4	Met87, Glu154, Asp183	3	3.05[Met87], 3.29[Glu154], 3.22[Asp183]	9	12
ZINC14490611	-8.3	Met87, Asn158, Asp183	3	3.05[Met87], 3.14[Asn158], 3.03[Asp183]	7	10

Corniculatusin	-8.2	Asn158, Asp183	3	3.03,3.26[Asn158], 2.98[Asp183]	10	13
ZINC13328057	-7.9	Met87, Asn158, Asp183	3	3.10[Met87], 3.07[Asn158], 3.07[Asp183]	8	11
Gossypetin 3,8-dimethyl ether	-7.7	Met87, Asn158, Ser336	3	2.83[Met87], 3.25[Asn158], 3.29[Ser336]	10	13
Gossypetin 3,7,8-trimethyl ether	-7.7	Met87, Asn158, Ser336	3	2.86[Met87], 3.31[Asn158], 3.26[Ser336]	9	12
(3S)-3,7-dihydroxy-8-methoxy-3-(3',4'-methylenedioxybenzyl)chroman-4-one	-7.6	Tyr111, Asp183, Thr185	3	2.95[Tyr111], 2.71[Asp183], 3.13[Thr185]	7	10

3'-hydroxyflindulatin	-7.6	Met87, Asn158, Ser336	3	2.81[Met87], 3.33[Asn158], 3.21[Ser336]	9	12
Aloe-emodin	-8.6	Met87, Glu154	2	3.08[Met87], 3.12[Glu154]	9	10
Onopordin	-8.4	Asn158, Asp183	2	2.85[Asn158], 3.23[Asp183]	9	11
ZINC05854400	-8.4	Met87, Asp183	2	2.84[Asp183], 2.89[Met87]	12	14
Isoscutellarein 8-methyl ether	-8.2	Met87, Asp183	2	2.95[Met87], 3.10[Asp183]	10	12
Sexangularetin	-8.2	Asn158, Asp183	2	3.16[Asn158], 2.97[Asp183]	8	10
4'-methyl gossypetin	-8.2	Asp183, Ser336	2	2.28[Asp183], 3.24[Ser336]	9	11
1,8-dihydroxy-3,5-dimethoxyxanthone	-8.1	Met87, Asn158	2	2.99[Met87], 3.30[Asn158]	8	10

Juglone	-7.3	Asp183, Thr185	2	2.80[Asp183], 3.23[Thr185]	7	9
Chrysophanol	-8.9	Met87	1	2.99[Met87]	8	9
Herbacetin	-8.5	Met87	1	3.01[Met87]	11	12
Bucegin	-8.3	Met87	1	3.04[Met87]	12	13
ZINC00058187	-7.6	Asn158	1	2.80[Asn158]	7	8
9-Hydroxy-α-Lapachone	-8.8	Asp183	1	3.03[Asp183]	7	8
Yangambin	-7.2	Thr185	1	3.32[Thr185]	12	13
Catechin	-7.7	None	0	None	11	11
α-Lapachone	-8.7	None	0	None	9	9

Table S2. Physicochemical Properties of 24 ligands and 4 known anti-Buruli ulcer drugs. Some of the drugs violated of Lipinski's rule. Known inhibitors as well as known drugs are in red.

Molecule	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	Lipinski #violations
Chrysophanol	254.24	0	4	2	0
Aloe-emodin	270.24	1	5	3	0
Herbacetin	302.24	1	7	5	0
Isoscutellarein	286.24	1	6	4	0
Onopordin	316.26	2	7	4	0
Betavulgarin	312.27	2	6	1	0
ZINC05854400	396.43	4	6	4	0
ZINC14490611	244.20	0	5	2	0
Bucegin	314.29	3	6	2	0
Isoscutellarein 8-methyl ether	300.26	2	6	3	0
Sexangularetin	316.26	2	7	4	0
Corniculatusin	244.20	0	5	2	0
4'-methyl gossypetin	332.26	2	8	5	0
1,8-dihydroxy-3,5-dimethoxyxanthone	288.25	2	6	2	0
Epitaxifolin	304.25	1	7	5	0
ZINC13328057	260.20	1	6	3	0
Catechin	290.27	1	6	5	0
Gossypetin 3,8-dimethyl ether	346.29	3	8	4	0
Gossypetin 3,7,8-trimethyl ether	360.31	4	8	3	0

ZINC00058187	314.29	3	6	2	0
Shikimic acid-4-O-gallate	340.28	4	9	6	1
(3S)-3,7-dihydroxy-8-methoxy-3-(3',4'-methylenedioxybenzyl)chroman-4-one	344.32	3	7	2	0
3'-hydroxyflindulatin	374.34	5	8	2	0
Gentisic acid 5-O-glucoside	316.26	4	9	6	1
Streptomycin	581.57	11	15	14	3
Ciprofloxacin	331.34	3	5	2	0
Rifampicin	822.94	5	14	6	3
Clarithromycin	747.95	8	14	4	2
Juglone	174.15	0	3	1	0
Paulownin	370.35	2	7	1	0
Yangambin	446.49	8	8	0	0
Alpha lapachone	242.27	0	3	0	0
9-hydroxy-alpha lapachone	258.27	0	4	1	0

Table S3. Physicochemical properties of the top 24 ligands and 4 known anti-Buruli ulcer drugs showing other physicochemical parameters. Known inhibitors and known drugs are in red.

Molecule	Fraction Csp3	TPSA	Consensus Log P	ESOL Log S	ESOL Class
Chrysophanol	0.07	74.6	2.38	-4.11	Moderately soluble
Aloe-emodin	0.07	94.83	1.5	-3.04	Soluble
Herbacetin	0	131.36	1.33	-3.55	Soluble
Isoscutellarein	0	111.13	1.72	-3.79	Soluble
Onopordin	0.06	120.36	1.72	-3.75	Soluble
Betavulgarin	0.12	78.13	2.44	-3.8	Soluble
ZINC05854400	0.26	111.13	4.3	-6.14	Poorly soluble
ZINC14490611	0.08	87.74	1.72	-3.53	Soluble
Bucegin	0.12	89.13	2.44	-3.97	Soluble
Isoscutellarein 8-methyl ether	0.06	100.13	2.12	-3.99	Soluble
Sexangularetin	0.06	120.36	1.74	-3.76	Soluble
Corniculatusin	0.08	87.74	1.72	-3.53	Soluble
4'-methyl gossypetin	0.06	140.59	1.37	-3.61	Soluble
1,8-dihydroxy-3,5-dimethoxyxanthone	0.13	89.13	2.16	-3.72	Soluble
Epitaxifolin	0.13	127.45	0.63	-2.66	Soluble
ZINC13328057	0.08	107.97	0.92	-2.74	Soluble
Catechin	0.2	110.38	0.85	-2.22	Soluble
Gossypetin 3,8-dimethyl ether	0.12	129.59	1.72	-3.81	Soluble
Gossypetin 3,7,8-trimethyl ether	0.17	118.59	2.11	-4.02	Moderately soluble
ZINC00058187	0.12	89.13	2.44	-3.97	Soluble

Shikimic acid-4-O-gallate	0.33	164.75	-0.08	-2.1	Soluble
3,7-dihydroxy-8-methoxy-3-(3',4'-methylenedioxybenzyl)chroman-4-one	0.28	94.45	1.91	-3.41	Soluble
3'-hydroxyflindulatin	0.21	107.59	2.49	-4.24	Moderately soluble
Gentisic acid 5-O-glucoside	0.46	156.91	-1.12	-0.94	Very soluble
Streptomycin	0.86	331.43	-5.83	1.8	Highly soluble
Ciprofloxacin	0.41	74.57	1.1	-1.32	Very soluble
Rifampicin	0.53	220.15	3.07	-8.18	Poorly soluble
Clarithromycin	0.95	182.91	2.13	-5.94	Moderately soluble
Juglone	0	54.37	1.36	-2.47	Soluble
Paulownin	0.4	75.61	2.1	-3.35	Soluble
Yangambin	0.5	73.84	3.04	-4.17	Moderately soluble
Alpha lapachone	0.33	43.37	2.56	-3.26	Soluble
9-hydroxy-alpha lapachone	0.33	63.6	2.34	-3.46	Soluble

Table S4. Toxicity results of 24 ligands with their respective structures predicted as AMES toxicity, carcinogens, and hERG I Inhibitor.

Compounds	AMES Category	hERG Category	Carcinogen
Chrysophanol	1	0	0
Aloe-emodin	1	0	0
Herbacetin	1	0	0
Isoscutellarein	1	0	0
Onopordin	0	0	0
Betavulgarin	0	0	0
ZINC05854400	0	0	0
ZINC14490611	1	0	0
Bucegin	0	0	0
Isoscutellarein 8-methyl ether	0	0	0
Sexangularetin	0	0	0
Corniculatusin	0	0	0
4'-methyl gossypetin	0	0	0
1,8-dihydroxy-3,5-dimethoxyxanthone	1	0	0
Epitaxifolin	1	0	0
ZINC13328057	1	0	0
Catechin	0	0	0
Gossypetin 3,8-dimethyl ether	0	0	0
Gossypetin 3,7,8-trimethyl ether	0	0	0
ZINC00058187	1	0	0
Shikimic acid-4-O-gallate	0	0	0
(3S)-3,7-dihydroxy-8-methoxy-3-(3',4'-methylenedioxybenzyl)chroman-4-one	0	0	0
3'-hydroxyflindulatin	0	1	0
Gentisic acid 5-O-glucoside	0	0	0
Juglone	1	0	0
Paulownin	0	0	0
Yangambin	0	0	0

Alpha lapachone	0	0	0
9-hydroxy-alpha lapachone	0	0	0